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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	12

PATRICK L. ...
ARNALL GOLDEN & ...
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ATLANTA GA 30309-345...

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1-27-97

☒ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-32 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-32 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☒ The drawing(s) filed on 3-3-1995 is/are objected to by the Examiner.
☒ The proposed drawing correction, filed on 1-27-1997 is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a))

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 11
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496 40517

1. The drawings are objected to because in Figure 2 the word "coupled" appears to mean "tethered"; the latter term is used throughout the disclosure and in the claims, and it is recommended that Applicants change the term "coupled" to "tethered" so as to remain consistent. Correction is required.

Applicant is required to submit a proposed drawing correction in response to this Office Action. Any proposal by the applicant for amendment of the drawings to cure defects must consist of two parts:

a) A *separate* letter to the Draftsman in accordance with MPEP § 608.02(r); and

b) A print or pen-and-ink sketch showing changes in *red ink* in accordance with MPEP § 608.02(v).

IMPORTANT NOTE: The filing of new formal drawings to correct the noted defect may be deferred until the application is allowed by the examiner, but the print or pen-and-ink sketch with proposed corrections shown in red ink is required in response to this Office Action, and *may not be deferred*.

With respect to the proposed drawing correction filed January 27, 1997, it is acceptable for Applicants to delete the title from the drawing. However, the word "coupled", which was the subject of the objection, occurs in the x-axis label.

2. Claims 1-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. The phrase "to enhance the rate of target cell growth" is indefinite because the term "enhance" is a relative term, but Applicants have not provided a basis with which to determine whether or not a particular rate of target cell growth is enhanced or not and thereby embraced within the scope of the claims. There are multiple possible bases for comparing growth rates, e.g., they can be compared to a composition which does not contain growth effector molecules, to a composition which contains growth effector molecules which are not tethered to a substrate, or to a composition containing tethered growth effector molecules at a relatively low concentration. In the absence of a specific basis, it is not possible to determine whether or not a growth rate is enhanced or not. At claim 5, line 1, the phrase "the polymer" is indefinite because it is not clear if this refers to the "biocompatible synthetic polymeric tethers" or to the biocompatible polymers which form the biocompatible substrate. For analogous reasons, the phrase "the polymer" at claim 6, line 1; claim 21, line 1; and claim 22, line 1; is indefinite.

3. Claim 8 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Independent claim 1 has been limited to require a synthetic polymeric tether. However, dependent claim 8 recites that the tether can be starch, which is a naturally-occurring material. Accordingly, dependent claim 8

does not further limit independent claim 1 but rather to some extent broadens it.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1-9, 13, 18-25, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clapper et al. Clapper et al. disclose a cell culture support consisting of a support material, a positively-charged molecule and a cell adhesion factor (see claim 7). It is disclosed that "the positively-charged molecule and the cell adhesion factor are covalently bound to one another and either the positively-charged molecule or the cell adhesion factor is covalently bound to the supporting surface" (see claim 7 (b)). Clapper et al. disclose that the support material can be prepared from many materials including synthetic polymers (see column 5, line 36 - 50), zirconia, alumina, glass and silica (see column 5, lines 52 - 53). It is disclosed that this cell culture support can be "in any suitable form, for instance, as membranes, tubes, microtiter wells, columns, hollow fibers, roller bottles, plates, dishes, and solid, hollow, or porous beads" (see column 5, lines 55 - 58). It is disclosed that the positively-charged molecule are synthetic (see column 7, line 44) and include carboxy methyl cellulose (see column 7, line 67). Clapper et al. disclose that the cell adhesion molecule include the extracellular matrix molecules "laminin, fibronectin, collagens (all types), vitronectin, and tenascin" (see column 6, lines 40 -

41[illegible]. Clapper et al. disclose that this cell culture support can be used for "cell culture of mammalian cells" (see column 1, line 21 . The cell adhesion molecules are present in amounts sufficient "to attract anchorage-dependent cells to the surface of the cell culture system, in order to allow the growth and/or spreading of such cells once attracted" (column 4, lines 63-67) and "to increase the rate at which such cells grow and spread on that surface" (column 6, lines 33-34). Because the cell adhesion molecules are ultimately covalently bound to the supporting surface, inherently they will not be able to be internalized by the cells.

6. Claims 10 - 12 and 26 - 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Clapper et al. Application of Clapper et al is the same as in the above rejection of claims 1-9, 13, 18-25, and 31. Clapper et al. disclose polymers as the positively charged molecules, but do not disclose backbone length of the polymers. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the positively charged molecules of Clapper et al. because degree of polymerization, i.e. backbone length, is an art-recognized, result-effective variable which is routinely determined and optimized in any art involving polymers.

7. Claims 1 - 9, 13 - 16, 18 - 25 and 31 are rejected under 35 U.S.C. § 103 a as being unpatentable over Herweck et al. in view

of Merrill (U.S. Patent No. 5,171,264). Herweck et al. disclose a device which can be used for stimulating the growth of eukaryotic blood cells (see Abstract and column 11, lines 24 - 49) and using this device as a "matrix and support upon which cellular matter is grown" (column 11, lines 26 - 27). This device consists of a substrate which can be manufactured from any suitable biocompatible material including fibers and polymers (see column 8, lines 44 - 57). Herweck et al. disclose that the substrate of the device can be shaped in any way needed for its required application (see column 4, lines 21 - 25). This device is also disclosed to be implantable (Abstract, line 1) and useful for treating a patient in need of cell growth (column 4, lines 39 - 40 and claim 28). Herweck et al. also disclose coating the substrate of the device with bioactive material such as platelet derived growth factor, epidermal growth factor, transforming growth factor, erythropoietin, and fibroblast growth factor (see claim 25 and column 12, lines 1 - 35). Herweck et al achieve an enhanced rate of target cell growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been made, and certain factors which can be present stimulate, i.e. enhance, endothelial cell growth (column 6, lines 23-29 and 33-36). Herweck et al. do not disclose biocompatible tethers which have one end covalently linked to the substrate and a growth effector molecule covalently linked to the other end. Merrill discloses star molecules composed of biocompatible, non-

thrombogenic, water-soluble polyethylene oxide (PEO)(see Abstract and column 1, line 21) which can have one arm covalently linked to a substrate thereby anchoring the molecule (see column 2, lines 11 - 14) and another arm covalently linked to a bioactive molecule (see column 5, lines 3 - 8 and claim 15). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a composition for use in stimulating the growth of eukaryotic blood cells consisting of a biocompatible substrate, biocompatible tethers and growth effector molecules as described by Herweck et al. using the polyethylene oxide star molecules for the biocompatible tether components as described by Merrill because the star molecules will prevent thrombogenesis from occurring when the device of Herweck et al. is implanted while still ensuring that the device remains coated with the bioactive material.

9. Claims 10-12 and 26-28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1-9, 13-16, 18-25, and 31 above and further in view of Merrill (J. Biomatter Sci. Polymer). Merrill discloses that the "length of each PEO chain corresponds to its molecular weight and typically range from about 1,000 to about 10,000" (see column 2, lines 56 - 59 . Merrill (J. Biomatter Sci. Polymer) discloses that the arms of PEO consist of varying numbers of ethylene oxide monomers CH_2OCH_2 see page 3 . The molecular weight of one of these

monomers is 44 daltons. Therefore, a PEO chain of 1,000 daltons would correspond to approximately 23 monomers corresponding to approximately 68 backbone atoms and a PEO chain of 10,000 daltons would correspond to approximately 680 backbone atoms. Therefore, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to design a composition for stimulating the growth of eukaryotic cells as described above and choosing a PEO chain length such that the backbone of the tether (i.e. from substrate to growth effector molecule would include 2 PEO chains and the central divinyl benzene molecule which is 8 atoms) could vary in length between about 136 and 1360 atoms as suggested by Merrill (J. Biomatter Sci. Polymer); optimization within this range would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made because Merrill '764 discloses chain length to be a result-effective variable.

9. Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Mikos. Neither Herweck et al. nor Merrill disclose a substrate which is biodegradable. Mikos discloses a "biodegradable, bioresorbable , three-dimensional template for repair and replacement of diseased or injured bone which provides mechanical strength to bone while also providing a guide for growth of bone tissue" (see Abstract, lines 1 - 4 .

Mikos discloses that "the implant is seeded with osteoblasts prior to implantation to provide regeneration sites for bone tissue" (see column 1, lines 64 - 63). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a cell growth composition outlined in the above rejection using a biodegradable material as described by Mikos because a patient in need of an implantable cell growth composition might only need it for a defined period of time and it would be less deleterious to the patient and more conducive to overall healing to have the cell growth composition biodegrade and be bioabsorbed so that further surgery and trauma to the patient would not be necessary.

10. Claims 29 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Naughton et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for parenchymal or stem cells. Additionally, neither Herweck et al. nor Merrill disclose using a cell growth composition for testing a compound for its effect on tissue. Naughton et al. disclose a "three-dimensional cell culture system which can be used to culture a variety of different cell" (see Abstract, lines 1 - 3). It is disclosed that this system can be used to culture parenchymal cells and stem cells (see column 13, last paragraph continuing to column 14 . Naughton et al. also

disclose using this system in cytotoxicity assays (see column 1, line 33 - 34). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to use the cell growth composition outlined in the above rejection to culture parenchymal and stem cells and to perform cytotoxicity assays, both as described by Naughton et al., because different cell culture methods are routinely sought in the cell culture art and because *in vitro* drug testing methods are preferable to *in vivo* drug testing methods so that animals are not harmed and cost is contained.

11. Claims 29 and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 1 - 9, 13 - 16, 18 - 25 and 31 above, further in view of Tomomura et al. Neither Herweck et al. nor Merrill disclose using a cell growth composition for hepatocytes. Tomomura et al. disclose that "rat hepatocytes in primary cultures lack the ability to proliferate" (Introduction, paragraph 1, lines 5 - 6) and that cultured rat hepatocytes are stimulated to replicate by addition of epidermal growth factor (see Abstract). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to use the cell growth composition outlined in the above rejection with epidermal growth factor as the growth effector molecule for cell culture of hepatocytes because such a cell culture would be useful because the liver is the "detoxification

center" of the body, however, when acting upon a compound, the liver may convert it to a form which is also toxic or in some way deleterious to the organism, so it would be useful to have long term cultures of hepatocytes to use for *in vitro* biotransformation reactions of chemicals, the biotransformation products of which could then be tested *in vitro* on other cultured cell types.

12. Claims 1-7, 9, 10, 13, 18-21, 23, 25, 26, 29, 30, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by the European Patent Application '733. The European Patent Application '733 teaches a carrier, e.g., a cellulose foam in the form of a cube, a rectangular parallelpiped, a globular shape, or chopped into small pieces (page 4, line 29 - page 5, line 14) to which is covalently attached cell adhesive factors such as fibronectin, vitronectin, fibrinogen, laminin, collagen, gelatin and fetuin (page 2, lines 56-57), i.e. extracellular matrix proteins, and cell growth factors such as EGF, PDGF, FGF, and IF (page 3, lines 22-25) through a spacer made from a biocompatible synthetic polymer such as a polyethyleneimine or a polyamino acid page 3, line 42 - page 4, line 25), i.e. a tether. Animal cells such as hepatocytes are cultured on the carriers (page 5, lines 18-28). The invention permits cells to be cultured in a higher density and larger quantity in comparison with conventional carriers page 5, lines 29-31). Because the cell adhesive factors and cell growth factors are covalently attached to the

carrier of the European Patent Application '733, inherently they will not be able to be internalized by the cells. Because the structure and chemical composition of carriers of the European Patent Application '733 are the same as is recited in Applicants' claims, and because of the higher cell density achieved by the European Patent Application '733, inherently the rate of target cell growth will be enhanced in the European Patent Application '733 to the same extent claimed by Applicants.

13. Claims 10-12 and 26-28 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '733. Application of the European Patent Application '733 is the same as in the above rejection of claims 1-7, 9, 10, 13, 18-21, 23, 25, 26, 29, 30, and 31. The European Patent Application '733 discloses spacer size to be an art-recognized result-effective variable (page 3, lines 51-53, and page 4, lines 21-23) but does not describe the size in terms of the number of backbone atoms. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the spacers of the European Patent Application '733 because spacer size is an art-recognized, result-effective variable as disclosed by the European Patent Application '733 and because determining spacer size will also result in determining the backbone length of the spacer.

14. Claims 1-10, 12-26, 28, and 31 are rejected under 35 U.S.C. 102 b as being anticipated by the WO Patent Application '616.

The WO Patent Application '616 teaches a support surface, e.g., a biocompatible polymer such as polyurethane, polyester, skin, or cellulose in any desired shape including shapes suitable for implantation (page 7, line 28 - page 9, line 16) to which is covalently attached biomolecules such as ECGF, FGF, PDGF, and collagen (page 7, lines 14-27) through a spacer preferably made from a polyethylene oxide at least 25 angstroms long, e.g. having a size of 1450 daltons which is equivalent to a backbone length of about 99 atoms (page 7, lines 2-8, and pages 20-24), i.e. a tether. Animal cells such as endothelial cells are cultured on the carriers (pages 20-24). The invention permits the loading density of biomolecules to a support surface to be increased (page 14, lines 27-30). Because the biomolecules are covalently attached to the support surface of the WO Patent Application '616, inherently they will not be able to be internalized by the cells. Because the structure and chemical composition of carriers of the WO Patent Application '616 are the same as is recited in Applicants' claims, and because of the higher biomolecule loading density achieved by the WO Patent Application '616, inherently the rate of target cell growth will be enhanced in the WO Patent Application '616 to the same extent claimed by Applicants.

15. Claims 11 and 27 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application '616. Application of the WO Patent Application '616 is the same as in the above

rejection of claims 1-10, 12-26, 28, and 31. The WO Patent Application '616 discloses spacer size to be an art-recognized result-effective variable (page 7, lines 2-5) but does not teach a spacer size of between 100 and 50,000 atoms. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal backbone lengths for the spacers of the WO Patent Application '616 because spacer size is an art-recognized, result-effective variable as disclosed by the WO Patent Application '616 and because determining spacer size will also result in determining the backbone length of the spacer.

16. Applicant's arguments filed January 27, 1997 have been fully considered but they are not deemed to be persuasive.

Applicants distinguish Clapper et al on the basis that the patent does not teach or suggest the use of growth effector molecules. However, Clapper et al teaches the use of several kinds of extracellular matrix molecules as pointed out in the rejection, and Applicants specifically claim extracellular matrix molecules as an example of growth effector molecules (see, e.g., claim 9). Accordingly, Clapper et al can not be distinguished on this basis. Clapper et al's invention specifically teaches that it results in an enhanced rate of growth - see column 6, lines 33-34.

The rejections based upon Herweck et al in view of Merrill '264 as the primary references are maintained. In their

response, Applicants have discussed certain deficiencies of Herweck et al. However, the reference is not applied alone under 35 U.S.C. 102 but rather is applied at least in combination with Merrill '264 under 35 U.S.C. 103. When the rejection is based on a combination of references, it is very difficult to show non-obviousness by such an attach on the individual references. In re Young, 159 USPQ 725 (CCPA 1968). What the references individually suggest or specifically disclose is not the appropriate inquiry; it is rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the relevant art. In re Sheckler, 169 USPQ 170 (CCPA 1971); In re McLaughlin, 170 USPQ 209 (CCPA 1971). In any event, Herweck et al do teach an enhanced rate of growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been made. This satisfies Applicants' claimed requirement for enhanced cell growth (and see the above rejection under 35 U.S.C. 112, second paragraph, where it noted that Applicants' claims do not specify the basis by which it is to be determined whether or not enhanced cell growth occurs).

The rejections based upon Herweck et al in view of Merrill '264 and further in view of Mikos and based upon Herweck et al in view of Merrill '264 and further in view of Naughton et al are also maintained. Again, Applicants have argued the deficiencies of a single reference rather than of the combination of three references including Mikos or including Naughton et al. Note

that Mikos is relied upon in the rejection to suggest biodegradable substrates, and Naughton et al is relied upon to suggest parenchymal or stem cells. With respect to Applicants' argument at page 9, lines 6-8, of the response, a reference never teaches away from modification on the basis that the reference's disclosure is "adequate"; otherwise, for example, a U.S. patent could never form the basis of a rejection under 35 U.S.C. 103 because by presumption all U.S. patents are "adequate" for their disclosed purposes.

With respect to Applicants' argument at page 9, lines 12-14, of the response, the examiner does not agree that there is no expectation of success in this art in the absence of actual studies. It is noted that Applicants have not conducted actual studies on all of their claimed embodiments (at least, actual studies of all the claimed embodiments have not been reported in the specification), yet the examiner does not believe that there is any reason to question Applicants' operability or enablement due to the lack of such actual studies. In any event, as noted above, the primary references relied upon by the examiner teach enhanced growth.

To the extent that Applicants may be arguing unexpected results at page 9, lines 17-19, of the response, unexpected results can not be relied upon to overcome a rejection based upon anticipation (see paragraph 5 above); the experiments do not appear to be a probative comparison with the closest prior art of

record, namely with Clapper et al and with Herweck et al; and the experiments are not commensurate in scope with Applicants' claims, i.e. a representative number of substrates, tethers, growth effector molecules, and concentrations have not been tested.

17. The European Patent Application '790 cited in the Information Disclosure Statement filed January 27, 1997 has not been considered because it is not in the English language and a concise explanation of its relevance was not provided. See 37 CFR 1.98(a).

18. This Office action is being made final even though there are new grounds of rejection based upon references cited in the Information Disclosure Statement filed January 27, 1997, because Applicants did not include a certification with the Information Disclosure Statement. See MPEP 600-94, column 2, second full paragraph (Rev. 2, July 1996).

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE

STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang, can be reached at (703) 308-0254. The fax number for Art Unit 1811 is (703) 305-3014 and the telephone number for the Group 180 receptionist is (703) 308-0196.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1811

JRussel
April 11, 1997